SPATIALLY ALIGNED CONJUGATED COMPOSITION HAVING A THIOETHER BOND LINKAGE

RESEARCH SUPPORT

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FIELD OF THE INVENTION

The present invention is concerned generally with the formation of spatially aligned conjugated compositions in which the component parts are linked in a controlled orientation by at least one thioether bond; and is particularly concerned with the controlled juncture of antigens or haptens to metallic oxide nanoparticles via at least one thioether bond and linkage to form a conjugate useful for a variety of immunological and other biomedical purposes.

BACKGROUND OF THE INVENTION

Among some of the earliest written records of man is an awareness that persons who recover from certain diseases cannot contract them again a second time. In today's terminology, such persons have become immune via a remarkably versatile set of adaptive processes which respond to an immense variety of infectious agents. Immune responses are encountered only in living vertebrates; and such immune responses constitute the principal means of defense against infection by pathogenic microorganisms.

In today's state of knowledge and technology, the infectious agents and the substances presented, produced or released by infectious agents are typically called "antigens". An almost limitless variety of macromolecules can behave as antigens—virtually all proteins; many polysaccharides; nucleoproteins, lipoproteins, and numerous synthetic polypeptides; and many small molecules if they are suitably linked to proteins or to synthetic polypeptides. Classically, an antigen has two properties: immunogenicity—the capacity to stimulate the formation of the corresponding antibodies and/or immune cells; and selectivity—the ability to react specifically with these antibodies or cells. Antigens are also distinct and different from "haptens" which, by definition, are not themselves immunogenic, but do react specifically with the appropriate corresponding antibodies or immune cells.

The term "immunogen" is often used for a substance or composition that stimulates the formation of the corresponding antibody in an organism able to respond. It is clear, however, that immunogenicity itself is not an intrinsic or inherent property of an infectious agent or a macromolecule. To the contrary, immunogenicity is dependent on the system and conditions employed in the introduction of the antigen into the body. One cardinal rule and condition is that the putative immunogen must be somehow recognized as alien, or foreign, or at least not as itself by the responding host.

In addition, for a variety of different public health reasons and medical reasons, man has employed immunogens and many different immunization procedures to increase active in-vivo resistance to infectious agents and to the products of pathogens. This has led to the ever-increasing study and development in the field of a unique problem: how to make and use an effective vaccine. By definition, a vaccine is a preparation used for immunization in which a suspension of infectious agents, some parts of them, or synthetic analogs of them, is given to a living subject in advance of a clinically

apparent condition to establish active resistance to an infection or disease. The prevention of clinical infections and pathological disease states via the use of vaccines is considered one of the most effective and available procedures to combat illness. Merely representative of the range and diversity of vaccines available today to prevent infectious disease in man are those listed by Table 1 below.

TABLE 1

Vaccines Preventing Infectious Disease in Man*

Disease	Immunogen
Diptheria	purified diptheria toxoid
Tetanus	purified tetanus toxoid
Smallpox	infectious (attenuated) virus
Yellow fever	infectious (attenuated) virus
Measles	infectious (attenuated) virus
Mumps	infectious (attenuated) virus
Rubella	infectious (attenuated) virus
Poliomyelitis	infectious (attentuated) virus or inactivated virus
Influenza	inactivated virus
Rabies	inactivated virus
Typhus fever	killed rickettsiae *Rickettsia prowazeki*
Typhoid and paratyphoid fevers	killed bacteria *Salmonelta typhi*, *S. schottmulleri*, and *S. paratyphi*
Pertussis	killed bacteria *Bordetella pertussis*
Cholera	crude fraction of cholera vibrios
Plague	crude fraction of plague bacillus
Tuberculosis	infectious (attenuated) mycobacteria (bacille Calmette-Guerin of "BCG")
Meningitis	purified polysaccharide from *Neisseria meningitidis*
Pneumonia	purified polysaccharides from *Streptococcus pneumoniae*

*Microbiology, [Davis, Dulbecco, Eisen & Ginsberg, editors], Harper & Row, 1988, p. 448.

Unfortunately, the development of vaccines and vaccination procedures which are effective against microbial antigens and infectious agents is a laborious and almost entirely empiric process. There are very few general rules which are reliable; and even these generalities are meager because they often do not apply uniformly or consistently. Among these are: that the material be antigenic—that is, that the composition contain chemical groupings which are not present in the living recipient and will become accessible to immunologically competent cells of the recipient which is to be immunized. In addition, it is essential that the material employed as a vaccine should have a sufficiently great molecular weight; in general, the larger a molecule is, the greater chance it will have of comprising foreign determinant groups on its surface. Also, it is often desirable that the substances in a vaccine be aggregated or be adsorbed on alum or other gels because these are usually more effective than soluble materials. The aggregated immunogens, by binding more effectively to cells in the living body, and by engaging more cell surface molecules on the specialized cells involved in generating immune responses, are often more stimulatory than dispersed or solute molecules; and the relatively slow rate of desorption from gels or emulsions maintains the antigen in tissues for longer periods of time. There also are variances and conditions regarding systemic versus local immunization procedures—the route of administration and the choice of site for injection being usually determined by convenience, but in some instances being limited by the very nature of the infectious agent, or vaccine efficacy itself, or by the nature or localization of the immune